

PMA Clinical Trial Design Work Sheet

2 ICD Study # 2 June 19, 1996

Regulatory Category: Category 2, Evolutional technology, PMA Supplement

4 **Device Description:** Add DDD pacing to commercially available ICD

Clinical Indication: Standard ICD indications + standard DDD indications

6 **Clinical Claim:** Reduced frequency of inappropriate therapy for atrial fibrillation (AF) at the appropriate stability setting

8 **Inclusion Criteria:** Patients with a history of paroxysmal AF or inducible into AF + indications for ICD and DDD pacing

10 **Primary Endpoint(s):** Rate (fraction) of appropriate treatment for atrial arrhythmia

Clinical Trial Design: Detection and appropriate treatment of atrial arrhythmias:

12 a) induced AF in the EP lab x 3 with 6, 30, 60 msec stability settings; and

14 b) spontaneous AF (after ICD implantation)

Type of Control: Randomized concurrent control, approved ICD + approved pacer

16 **Sample size calculation:** Based on AF detection rate (appropriate therapy decisions)

Type I error: $\alpha = 0.05$ (2 tail), $\beta = 0.2$ (power = 0.8),

18 Estimated success: 85% (new) vs. 75% (control)¹

Pooled standard deviation = 17%

20 Sample size (effectiveness)² = 46 patients / group

Expected attrition (dropout rate): 30%

22 **Num pats / arm:** Enroll: 130 total (65 patients / group)

Follow-up (#, duration): 40 patients / group to 3 mos

24 20 patients / group to 6 mos

26 1. Higgins SL, et al: Stability: an ICD detection criterion for discriminating atrial fibrillation from ventricular tachycardia. J Cardiovasc Electrophysiol 1995; 6: 1081-8. [51]

28 2. Borenstein M, Cohen J: Statistical Power Analysis: A Computer Program. Lawrence Erlbaum Associates, Hillsdale, NJ, 1988, 187 pages. [54]

PMA Clinical Trial Design Work Sheet

2 **ICD Study #** 3 June 19, 1996

Regulatory Category: Category 2, Evolutional technology, PMA Supplement

4 **Device Description:** Change in lead system which may alter pacing threshold, e.g., steroid tip, smaller electrode.

6 **Clinical Indication:** Standard ICD RV lead indication

Clinical Claim: Chronic pacing thresholds are equivalent to previous devices.

8 **Primary Endpoint(s):** Step-down pulse-width thresholds at nominal pacing-voltage output.

10 **Study Design:** Two groups, implanted, measuring thresholds at implant, 24 hours, 1 month, and 3 months after implant.

Type of Control: Concurrent randomized, currently available lead.

12 **Sample Size Calculation:**

14 Control rate:0.10 ms @ implant, 0.20 ms @ 1 Month, 0.18 ms @ 6 months

Critical difference:5%

16 Type I error rate:5%

Power:80%

18 Test statistic/estimator:Likelihood ratio/Generalized estimating equation estimator^{1,2}

20 **Number of Patients:** 160 (80/group)

Follow-up: Duration:Average 3 months

22 Reporting Interval:Implant, 1 month, 3 months, 6 months

24 1. Lee EW, Dubin N: Estimation and sample size considerations for clustered binary responses. *Statistics Medicine* 1994; 13: 1241-52. [52]

26 2. Blackwelder WC: "Proving the null hypothesis" in clinical trials, *controlled clinical trials* 1982; 3: 345-53. [19]

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PMA Clinical Trial Design Work Sheet

2 **ICD Study #** 4 June 19, 1996

Regulatory Category: Category 2, Evolutional technology, PMA Supplement

4 **Device Description:** New ICD that uses novel antitachycardia therapy, e.g., high-output pacing pulses

6 **Clinical Indication:** Standard ICD indication

Clinical Claim: New antitachycardia pacing is equivalent against spontaneous VT

8 **Primary Endpoint(s):** Effectiveness rate of therapy against spontaneous VT episodes.

10 **Study Design:** Parallel groups, one using control device, the other using new device, implanted and followed every three months for spontaneous events.

12 **Type of Control:** Randomly assigned, currently available device. Historical controls may be used with adequate justification.

14 **Sample Size Calculation:**

Control rate:99% effectiveness

16 Critical difference:20%

Type I error rate:5%

18 Power:80%

20 Test statistic/estimator:Likelihood ratio/Generalized estimating equation estimator^{1,2}

Number of Patients: 86 (43 / group)

22 **Follow-up:** Duration: Estimated average 3 months to obtain adequate number of events.

24 **Reporting Interval:** Implant, 1 month, 3 months, 6 months

26 1. Lee EW, Dubin N: Estimation and sample size considerations for clustered binary responses. *Statistics Medicine* 1994; 13: 1241-52. [52]

28 2. Blackwelder WC: "Proving the null hypothesis" in clinical trials, *controlled clinical trials* 1982; 3: 345-53. [19]

PMA Clinical Trial Design Work Sheet2 ICD Study # 5

June 19, 1996

Regulatory Category: Category 2, Evolutional technology, PMA Supplement

4 **Device Description:** Change in the size, shape, or impedance of the defibrillation
 6 electrodes or pathways, e.g., SVC lead with longer coil or putting
 both AV and SVC coil on the same lead.

Clinical Indication: Standard ICD lead system indications8 **Clinical Claim:** New lead equivalent in efficacy

10 **Primary Endpoint(s):** Adequate defibrillation threshold criterion met at implant. Record
 outcome at each shock per DFT protocol.

Study Design: Two groups, implanted, measuring thresholds at implant.12 **Type of Control:** Randomly assigned, currently available lead.**Sample Size Calculation:**

14 Control Rate:80% success

Critical Difference:20%

16 Type I error rate:5%

Power:80%

18 Test statistic/estimator:Chi-square/Proportion¹**Number of Patients:** 246 (123/group)20 **Follow-up:** Duration: No minimum.

Reporting Interval: Implant

22 2. Lee ET: Statistical Methods for Survival Data Analysis, John Wiley, NY, 1992. [9]

PMA Clinical Trial Design Work Sheet

2 ICD Study # 6 June 19, 1996

Regulatory Category: Category 2, Evolutional technology, PMA Supplement

4 **Device Description:** Change in the defibrillation pathway or electrode system, e.g., can-as-electrode modification of a standard ICD.

6 **Clinical Indication:** Standard ICD indications

Clinical Claim: New lead equivalent in efficacy

8 **Primary Endpoint(s):** Effectiveness of defibrillation of spontaneous VF episodes.

10 **Study Design:** Two groups implanted, measuring spontaneous VF effectiveness rates for 3 months.

Type of Control: Randomly assigned, currently available device.

12 **Sample Size Calculation:**

Control rate:98.6%

14 Critical difference:20%

Type I error rate:5%

16 Power:80%

18 Test statistic/estimator:Likelihood ratio/Generalized
estimating equation estimator^{1,2}

Number of Patients: 86 (43/group)

20 **Follow-up:** Duration: Estimated average of 3 months to obtain adequate number of events.

22 Reporting Interval: Implant, 1 month, 3 months, 6 months

24 1. Lee EW, Dubin N: Estimation and sample size considerations for clustered binary responses. Statistics
Medicine 1994; 13: 1241-52. [52]

26 2. Blackwelder WC: "Proving the null hypothesis" in clinical trials, controlled clinical trials 1982; 3: 345-53.
[19]

Postmarket Surveillance Study Design Work Sheet

2 **ICD Study #** 7-RPS June 19, 1996

Regulatory Category: Category 5, Evolutional technology, PMA Supplement

4 **Device Description:** Approved ICD, no change in pulse generator or lead system.

6 **Clinical Indication:** New ICD indication, e.g., s/p MI, asymptomatic, EF \leq 35%,
inducible, nonsuppressible VT

Clinical Claim: Equivalent to ICD systems with this indication

8 **Preclinical testing:** Engineering equivalence to devices with this indication

10 **Primary Endpoint(s):** Two year mortality (all cause, sudden cardiac death, perioperative
mortality)

Study Design: Multicenter, prospective observational study

12 **Type of Control:** Premarket cohort, historical, e.g., MADIT cohort

Sample Size Calculation:

14 Historical Control Rate:.....87% [79%-95%] (N=95)

Critical Difference:13%

16 Type I error rate:.....5%

Power:80%

18 Test statistics/estimator:.....Kaplan-Meier survival

Number of Patients: 120 patients

20 **Follow-up:** Duration: Death or 24 months to primary end-point

Reporting Interval: 6 Months

22 1. Lee ET: Statistical Methods for Survival Data Analysis, John Wiley, NY, 1992. [9] using the binomial
approximation

24 2. Blackwelder WC: "Proving the null hypothesis" in clinical trials, controlled clinical trials 1982; 3: 345-53.
[19]

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PMA Clinical Trial Design Work Sheet2 ICD Study # 8

June 19, 1996

Regulatory Category: Category 2, Evolutional technology, PMA Supplement

4 **Device Description:** Change in the implant location for a device or the fixation method
 6 for a lead, e.g., change from screw-in to tined leads or move to pectoral location.

Clinical Indication: Standard ICD indications.

8 **Clinical Claim:** Equivalent complication-free cumulative survival at 3 months
 between the investigational device and the control.

10 **Primary Endpoint(s):** Cumulative 3-month complication-free survival. Complications are
 defined as clinical events requiring invasive intervention.

12 **Study Design:** Two parallel groups implanted, measuring complication-free
 cumulative survival at 3 months.

14 **Type of Control:** Concurrent randomized vs. approved device

Sample Size Calculation:

16 Control Rate:.....93.5%

Critical Difference:20%

18 Type I error rate:.....5%

Power:80%

20 Test statistics/estimator:.....Kaplan-Meier¹

Number of Patients: 246 (123 / group)

22 **Follow-up:** Duration: Average of 3 months in order to obtain adequate number
 of events.

24 Reporting Interval: 3 Months

26 1. Lee ET: Statistical Methods for Survival Data Analysis, John Wiley, NY, 1992. [9] using the binomial
 approximation

28 2. Blackwelder WC: "Proving the null hypothesis" in clinical trials, controlled clinical trials 1982; 3: 345-53.
 [19]

PMA Clinical Trial Design Work Sheet2 **ICD Study #** 9

June 19, 1996

Regulatory Category: Category 2, Evolutional technology, PMA Supplement4 **Device Description:** Changes in sensing system or detection algorithm (e.g., electrogram width algorithm).6 **Clinical Indication:** Detection of VT/VF in standard ICD indications, at the same time rejecting NSR/SVT.8 **Clinical Claim:** Equivalent sensitivity for detecting target episodes (VT/VF).10 **Primary Endpoint(s):** Relative sensitivity, defined in reference to existing detection algorithm: (True VT new)/(True VTold). Relative sensitivity can be greater than 1.12 **Study Design:** Within patient study based on the classification of events by both the new and old algorithm. Follow-up for spontaneous events, both appropriately and inappropriately targeted by the device. Based on number of patients with events and distribution of events across patients.
14
1618 **Type of Control:** Each patient episode serves as its own control, cross-classified by new and existing algorithms.**Sample Size Calculation:**

20 Control rate:.....100%

Critical difference:.....2%

22 Type I error rate:.....5%

Power:80%

24 Test statistic/estimator:.....Likelihood ratio/Generalized
estimating equation estimator^{1,2}26 **Number of Patients:** Estimated 110 patients/300 events**Follow-up Duration:** Average of 3 months to obtain adequate number of events.

28 Reporting Interval:3 months

30 1. Lee EW, Dubin N: Estimation and sample size considerations for clustered binary responses. Statistics
Medicine 1994; 13: 1241-52. [52]32 2. Blackwelder WC: "Proving the null hypothesis" in clinical trials, controlled clinical trials 1982; 3: 345-53.
[19]

June 19, 1996

Postmarket Surveillance Study Design Work Sheet2 ICD Study # 9-RPS

June 19, 1996

Regulatory Category: Category 2, Evolutional technology, PMA Supplement4 **Device Description:** Changes in sensing system or detection algorithm**Clinical Indication:** Rejection of SVT/NSR in standard ICD indications.6 **Clinical Claim:** Equivalent specificity for rejecting non-target episodes (SVT/NSR).8 **Primary Endpoint(s):** Incremental specificity, defined in reference to inappropriately detected episodes under the old system. Incremental specificity can be negative.10 **Study Design:** Self-controlled study based on the classification of events by both
12 the new and old algorithm. Follow-up for spontaneous events, both
14 appropriately and inappropriately targeted by the device. Based on
number of patients with events and distribution of events across
patients.16 **Type of Control:** Each patient episode serves as its own control, cross-classified by
new and existing algorithms.**Sample Size Calculation:**

18 Control rate:.....0%

Critical difference:.....20%

20 Type I error rate:.....5%

Power:80%

22 Test statistic/estimator:.....Chi-squared/Incremental specificity

Number of Patients: 20 patients24 **Follow-up:** Duration: At least 3 months

Reporting Interval: 3 Months

Postmarket Surveillance Study Design Work Sheet

2 ICD Study # 10-RPS

June 19, 1996

Regulatory Category: Category 5, Evolutional technology, PMA Supplement

4 **Device Description:** Downsized only, e.g., smaller capacitor or battery

Clinical Indication: Standard ICD indications

6 **Study Objectives:** Monitor long-term safety and effectiveness in the general population under actual conditions of use.

8 **Primary Endpoint(s):**

Mortality (all cause, sudden cardiac death, perioperative mortality)

10 Complication/failure rates for generators with attribution of failure to the level of the new component

12 Explant rates and longevity

Observations

14 **Study Design:** Multicenter, prospective observational study

16 **Type of Control:** Each patient episode serves as its own control, cross-classified by new and existing algorithms.

18 **Sample size calculation:** For every model (or group of pooled models), a study size should at a minimum, be 90% likely to detect a doubling in adverse event rate of 1% or more at 3 years.

20 The sample size estimate is based on an AE rate of 1%. If the standard AE rate is lower or higher the estimate will vary accordingly.

22 **Number of patients:** 300 to 400

24 **Follow-up duration:** 5 years -- Thorough follow-up on appropriate schedule is necessary to assure the quality of the "denominator".

26 **Reporting interval:** Every 6 months for the duration of the study

28 1. Lee EW, Dubin N: Estimation and sample size considerations for clustered binary responses. Statistics Medicine 1994; 13: 1241-52. [52]

30 2. Blackwelder WC: "Proving the null hypothesis" in clinical trials, controlled clinical trials 1982; 3: 345-53. [19]

Preclinical Design Work Sheet

2 ICD Study 11-Pre June 19, 1996

4 **Regulatory Category:** Category 1, Novel technical issue, Effectiveness and Safety data required, Original PMA

6 **Device Description:** Atrial defibrillator

8 **Clinical Indication:** Atrial fibrillation, symptomatic on maximally tolerated medical therapy

10 **Clinical Claim:** Superior to medical management

12 **Testing Objectives:** *In vitro* demonstration of safety and effectiveness by test result conformance to design specifications.

14 **Bench Testing:** All components, subassemblies and circuits including battery and capacitor as outlined in Section II.A.1-3.

16 Fully test any new lead system associated with the defibrillator as outlined in Section II.A.4.

18 **Software:** Functionally test finished ICD system and programmers under all appropriate environmental conditions including electromagnetic compatibility (EMC) testing (Section II.A.5-9).

20 **Biocompatibility:** Document and fully test the software used in the ICD system including hazard analysis and validation (Section II.B).

22 **Biocompatibility:** Document Materials not previously approved which contact biological tissues should be tested as per Section II.C.

24 **Animal Studies:** ICDs have already reached advanced levels of technical development and may not require animal testing in this instance. Significant future design changes and technical advancements of ICDs and/or of the component parts thereof may require safety testing in animals.

26 Such animal study protocols should be discussed with FDA review personnel prior to commencing animal experiments.

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June 19, 1996

PMA Clinical Trial Design Work Sheet

2 ICD Study # 11 June 19, 1996

4 **Regulatory Category:** Category 1, Novel technical issue, Effectiveness and Safety data required, Original PMA

Device Description: Atrial defibrillator

6 **Clinical Indication:** Atrial fibrillation, symptomatic on maximally tolerated medical therapy

8 **Clinical Claim:** Superior to medical management

10 **Preclinical Studies:** Complete bench testing and appropriate animal studies will be required

12 **Primary Endpoint(s):** Survival (all causes and cardiac) at 6 mos and 1 year, Death from cardiac causes will be 20% lower

Clinical Trial Design: ICD vs. medical with 6 mo rescue

14 **Type of Control:** Concurrent controls, equal number of patients receive ICD and medical treatment, prospective randomization

16 **Sample size calculation:**

18 Effectiveness: $\alpha = 0.05$ (two tailed), $\beta = 0.2$ (power = 0.8), assume 20% lower mortality at 6 mos

Sample size (effectiveness)¹ (0.05, 0.2, 20%) = 148

20 Safety: 95% CI adverse event < 2%

Sample size (safety)² (95%, 2%) = 150

22 **Num pats / arm:** 150 (total = 300), assuming 10% dropout, enroll 165/arm (total = 330)

24 **Follow-up (#, duration):** 150 x 6 mo, 75 x 1 year

Postmarket Surveillance Study Design Work Sheet

ICD Study # 11-RPS

June 19, 1996

Regulatory Category: Category 1, Novel technical issue, Effectiveness and Safety data required, Original PMA

Device Description: Atrial defibrillator

Clinical Indication: Atrial fibrillation, symptomatic on maximally tolerated medical therapy

Study Objectives: Monitor long-term safety and effectiveness in the general population under actual conditions of use.

Primary Endpoint(s):

- Mortality (all cause, sudden cardiac death, perioperative mortality)
- Complication/failure rates for generator and leads
- Explant rates and longevity
- Observations

Study Design: Multicenter, prospective observational study

Type of Control: Premarket cohort or historical

Sample size calculation: For every model (or group of pooled models), a study size should at a minimum, be 90% likely to detect a doubling in adverse event rate of 1% or more at 3 years.

The sample size estimate is based on a Known Standard AE rate of 1%. If the standard AE rate is lower or higher the estimate will vary accordingly.

Number of patients: 300 to 400

Follow-up duration: 5 years -- Thorough follow-up on appropriate schedule is necessary to assure the quality of the "denominator".

Reporting interval: Every 6 months for the duration of the study

PMA Clinical Trial Design Work Sheet

2 ICD Study # 12 June 19, 1996

Regulatory Category: Category 2, Evolutional technology, PMA Supplement

4 **Device Description:** Change in the defibrillation pathway or electrode system, e.g., can-
as-electrode modification of a standard ICD.

6 **Clinical Indication:** Standard ICD indications

Clinical Claim: New lead system equivalent in efficacy

8 **Primary Endpoint(s):** Effectiveness of defibrillation against induced VF episodes.

10 **Study Design:** Two parallel groups, measure inductions at 1 and 3 months after
implant.

Type of Control: Randomly assigned, currently available device.

12 **Sample Size Calculation:**

Control rate:.....80% 1st shock @ 24j

14 Critical difference:.....12%

Type I error rate:.....5%

16 Power:80%

18 Test statistic/estimator:.....Likelihood ratio/Generalized
estimating equation estimator^{1,2}

Number of Patients: 300 (150/group)

20 **Follow-up:** Duration:At least 3 months

22 Reporting Interval:Inductions at 1 month (optional) and
3 months, follow-up at 6 months and
each 6 months thereafter.

24 1. Lee EW, Dubin N: Estimation and sample size considerations for clustered binary responses. Statistics
Medicine 1994; 13: 1241-52. [52]

26 2. Blackwelder WC: "Proving the null hypothesis" in clinical trials, controlled clinical trials 1982; 3: 345-53.
[19]

PMA Clinical Trial Design Work Sheet2 ICD Study # 13

June 19, 1996

Regulatory Category: Category 2, Evolutional technology, PMA Supplement4 **Device Description:** Existing ICD with VVI modified to DDD pacing**Clinical Indication:** Standard ICD indications6 **Clinical Claim:** The addition of an atrial lead reduces frequency of inappropriate therapy for atrial fibrillation (AF) at the appropriate stability setting8 **Inclusion Criteria:** Patients with a history of paroxysmal AF or inducible into AF**Primary Endpoint(s):** Atrial arrhythmia discrimination of induced arrhythmias10 **Clinical Trial Design:** Dose response design: compare 6, 30, 60 msec stability settings**Type of Control:** Within patient design (patient is own control)12 **Sample size calculation:** Based on discrimination rate (appropriate therapy decisions)Type I error: $\alpha = 0.05$ (one tail), $\beta = 0.2$ (power = 0.8),14 Estimated success: 98% vs. 91%¹

Critical difference: 5%

16 Sample size (effectiveness)² (0.05, 0.2, 5%) = 43

Expected attrition (dropout rate): 50%

18 Planned enrollment: 65 patients

Num pats / arm: enroll 65 patients total20 **Follow-up (#, duration):** 3 months

22 1. Higgins SL, et al: Stability: an ICD detection criterion for discriminating atrial fibrillation from ventricular tachycardia. J Cardiovasc Electrophysiol 1995; 6: 1081-8. [51]

24 2. Blackwelder WC: "Proving the null hypothesis" in clinical trials, controlled clinical trials 1982; 3: 345-53. [19]

26